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Prospective study of tooth loss and incident esophageal and gastric cancers in China

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Abstract

Objective: To determine the association between tooth loss and the risk of developing esophageal squamous cell carcinoma, gastric cardia adenocarcinoma, or gastric non-cardia adenocarcinoma in a prospective study.
Methods: Cox proportional hazards regression was used to examine these associations in a 28,868-person cohort followed prospectively for 5.25 years. The baseline questionnaire included questions regarding tooth loss, and individuals reporting lost teeth had their teeth counted by study personnel. The analytic cohort included 620 esophagus, 431 gastric cardia, and 102 gastric non-cardia cancer cases.
Results: Tooth loss was associated with a significantly elevated risk of developing all three cancers. When examined as median splits, tooth loss was associated with a relative risk (RR) (95% confidence interval, CI) of 1.3 (1.1–1.6) in the esophagus, 1.3 (1.0–1.6) in the gastric cardia, and 1.8 (1.1–3.0) in the gastric non-cardia. Further analysis demonstrated that this increased risk was most strongly associated with the loss of the first few teeth and was primarily confined to the younger members of our cohort.
Conclusions: In this cohort tooth loss increased the risk of developing upper gastrointestinal cancer. We hypothesize that this may be related to alterations in oral bacterial flora and subsequent increases in the *in-vivo* production of carcinogens such as nitrosamines.

Introduction

Poor oral health has been associated with increased risk of cancer at several sites. Oral cancer has been associated with both tooth loss and poor oral hygiene in a number of studies, independent of age, tobacco consumption, and alcohol consumption, the primary identified risk factors for this cancer [1–3]. A single retrospective study, conducted in Shanxi Province, People's Republic of China, found that regular tooth brushing reduced the risk of esophageal cancer, with an odds ratio (OR) (95% confidence interval (CI)) = 0.2 (0.1–0.5) [4]. An association between oral hygiene and/or tooth loss and gastric cancer has also been noted in retrospective studies conducted in Japan, Turkey, and Germany [5–7].

The people of Linxian, People's Republic of China, form a predominantly rural population with some of the highest rates of esophageal and gastric cardia cancer in the world, but oral cancer is relatively uncommon [8]. Dental care is essentially unavailable in Linxian, early tooth loss is common, and dentures are rare. In the current study, prospective data collected as part of a previously described nutrition intervention trial in Linxian [9, 10] were used to assess the relationship between tooth loss and subsequent risk of esophagus, gastric cardia, or gastric non-cardia cancers.

Methods

Data collection and cohort characteristics

A full description of the Linxian General Population Trial cohort has been published previously [9, 10].

Briefly, 29,584 cancer-free individuals, aged 40–69 years, were recruited from the general population of four Linxian communes in 1985. All participants were interviewed to assess lifestyle, dietary patterns, and medical history. Vitamin/mineral supplements were provided from March 1986 through May 1991. Active surveillance of the entire cohort during this period, including monthly contact of all subjects by village health workers and periodic review of medical records at all medical facilities in Linxian and the Cancer Hospital in the prefecture capital of Anyang, allowed essentially complete case ascertainment, with little or no loss to follow-up. Cases were reviewed by an International Endpoints Review Committee; a panel of expert cytologists, pathologists, and radiologists from the US and the People's Republic of China. This panel reviewed and confirmed 85% of the cancer diagnoses, virtually all of which were based on histology, cytology, or X-ray. This study was approved by the Institutional Review Boards of the US National Institutes of Health and the Cancer Institute of the Chinese Academy of Medical Sciences.

As part of the baseline interview, trial participants were asked if they had lost any permanent teeth. Those who answered yes were asked to recall the age at which the first permanent tooth was lost. Interviewers then counted the number of remaining teeth of all those who had reported missing teeth. Those who reported no missing teeth were assumed to have 32 teeth.

Variable definitions

Three primary independent tooth loss variables were defined for our analysis. The first tooth loss variable, lost teeth, was defined as a dichotomous variable, any *versus* no teeth lost. Second, the number of lost teeth was determined by subtracting the number of remaining teeth from 32 and used as a continuous variable (per 10 teeth lost) and as a categorized median split. Third, age at first loss was used as a continuous variable.

Age at baseline was represented both by age categories and as a continuous variable. Age categories were based on those previously defined for use in this cohort, <50, 50–59, and ≥ 60 years. We also created three dummy variables in which a person's score represented the distance, in years, from the bottom of the age category, 40, 50, or 60 years, respectively.

Use of alcohol was dichotomized into none or any alcohol consumed in the previous 12 months. Use of tobacco was dichotomized into never or ever use of cigarettes or pipe regularly for ≥ 6 months. Person-years of observation were calculated by determining the number of weeks from the start of the intervention, March 1986, until the date of cancer diagnosis, death from another cause, or the end of the intervention, May 1991, followed by converting the number of weeks to years.

Dietary variables were constructed for 15 food categories based on information collected from the baseline questionnaire. Number of times consumed per year was calculated for: persimmon bread, moldy bread, foods cooked in oil, meat, and eggs. Separately for the summer/autumn and winter/spring seasons, we calculated frequency of consumption/year for: fresh vegetables, dried vegetables, pickled vegetables, fresh fruit, and dried fruit.

Four variables were also constructed to represent general health, based on information from the baseline questionnaire: presence of an illness that precludes work, number of colds/flu in the previous 12 months, a summary variable for the number of yes answers to a list of 16 diseases (hepatitis, anemia, goiter, etc.), and a summary variable for the number of yes answers to a list of 18 conditions (chest pain, night blindness, insomnia, etc.).

Cancer endpoints

Approximately 1 year passed between the baseline interviews and the commencement of the vitamin/mineral intervention. Individuals who died or developed cancer during this interval were excluded from the General Population Trial and our analysis. Cancer diagnoses were assigned to anatomical subsites as follows: esophageal cancers were squamous cell carcinomas that originated in the esophagus, gastric cardia cancers were adenocarcinomas that occurred in the proximal 3 cm of the stomach, and gastric non-cardia tumors were adenocarcinomas that occurred below the proximal 3 cm of the stomach. Adenocarcinomas localized to the gastro-esophageal junction were treated as gastric cardia cancers because of the nearly-complete absence of esophageal adenocarcinomas in the Linxian population [11]. In China, esophageal squamous cell carcinoma and gastric cardia adenocarcinoma have traditionally been classified as a single disease because of the difficulty in distinguishing the two tumors clinically, so this combined category (referred to as esophagus/cardia) was also analyzed. A small number of non-gastrointestinal cancers were identified in the cohort and have been included under the rubric non-cases.

During the 5.25 years of intervention and follow-up, 639 esophageal squamous cell carcinomas, 438 gastric cardia adenocarcinomas, and 104 gastric non-cardia adenocarcinomas occurred. No information on tooth

loss was collected for 104 individuals, no data on current tooth number were collected for 68 individuals, and 547 participants did not provide information on age at first loss. Individuals without complete tooth loss information were excluded from the entire analysis, a total of 716 (2.4%) of the 29,584 original cohort members.

Statistical methods

Statistical analyses were carried out using the SAS/STAT statistical software package (Cary, NC). All *p*-values were derived from two-sided tests and statistical significance was set at $p < 0.05$.

Proportions or distributions for age and tooth loss variables for each cancer site were compared to non-cases using chi-square or Wilcoxon rank-sum tests. Associations between tooth loss and both continuous and categorical variables were assessed using linear regression.

Relative risks and 95% CI values were calculated using Cox proportional hazards regression stratified on age category. Within each stratum an additional stratum-specific age term for continuous age was used to adjust for variation in age within stratum. In addition to age, sex, tobacco use, and alcohol use were always included in the models. Confidence intervals were Wald-based. Nested models were compared using the likelihood ratio χ^2 test (LR χ^2). The proportional hazards assumption of the Cox model was tested in each model by adding a time-dependent covariate (tooth loss $\times$ follow-up time) and its significance was tested using the LR χ^2. The assumption was valid in all models tested.

For continuous measures of tooth loss, deviations from log linearity were tested by adding quadratic terms to the full regression model and testing significance with a 1 degree of freedom LR χ^2. Statistical interactions between age and tooth loss, sex and tooth loss, and intervention group and tooth loss were evaluated by adding a new term to the model which represented the product of the two potential interacting variables and testing the significance using the LR χ^2.

Results

Table 1 shows selected characteristics of the cohort members, including the number of cases of upper gastrointestinal cancer which occurred during the 5.25-year follow-up period. The final number of incident cancer cases included in this analytical cohort was 620 for the esophagus, 431 for the gastric cardia, 102 for the gastric non-cardia, and 1051 for the esophagus/cardia. The median age at baseline for cases was significantly higher ($p < 0.01$) at each cancer site than that of the non-cases. Among women, tobacco and alcohol use was rare, with 0.2% reporting ever using tobacco for $\geq$6 months and 10.2% reporting any alcohol consumption in the previous 12 months. Among men, 67.2% reported tobacco use and 40.2% reported any alcohol use. Tooth loss was common when examined in the entire cohort, with 74% of participants having lost at least one permanent tooth, median number of teeth lost (interquartile range, IQR) was six (15) and the median age (IQR) at first permanent tooth loss was 39 (15) years. For each cancer site, the proportion with lost teeth, the median number of teeth lost, and the median age at first loss were higher and statistically different from non-cases ($p < 0.01$).

We examined several factors by linear regression for their association with number of teeth lost, and the results are presented in Table 2. Age was the only factor which correlated strongly with the number of teeth lost. Other factors, including general health status and consumption of a variety of dietary components, had only very small associations with the number of teeth lost.

Table 1. Analytical cohort characteristics and tooth loss variables by tumor location

Tumor location	Esophagus	Gastric cardia	Non-cardia	Esophagus/cardia	Non-cancer
Number of participants	620	431	102	1051	27,715
Age: median (IQR)[a]	57 (12)	58 (11)	59 (10)	57 (12)	51 (15)
Sex (% male)	51	60	76	55	45
Tobacco use[b] (% ever)	40	43	54	41	30
Alcohol use[c] (% yes)	24	22	27	23	24
Lost teeth (% yes)	85	84	90	85	74
Number of teeth lost: median (IQR)	9 (17)	10 (18)	11 (15)	10 (17)	6 (14)
Age at first loss: median (IQR)	42 (16)	43 (17)	43 (17)	42 (16)	40 (14)

[a] IQR = Size of interquartile range (25th percentile–75th percentile).
[b] Tobacco use defined as ever use of tobacco products for $\geq$6 months.
[c] Alcohol use defined as any consumption of alcohol in the previous 12 months.

Table 2. Predictors of number of teeth lost. Regression coefficient, R^2, and *p*-value for different potential correlates of tooth loss[a]

Variable	β-Coefficient	R^2 (%)	*p*-Value
Age	0.59	26.3	< 0.0001
Fresh fruit/summer	−0.038	1.1	< 0.0001
Sex	−1.7	0.7	< 0.0001
Alcohol use	−0.75	0.29	< 0.0001
Dried fruit/winter	−0.052	0.23	< 0.0001
Dried fruit/summer	−0.033	0.21	< 0.0001
Fresh vegetables/winter	−0.0036	0.21	< 0.0001
Meals with meat	−0.015	0.20	< 0.0001
Dried vegetables/winter	0.0038	0.16	< 0.0001
Illness precluding work	1.2	0.12	< 0.0001
Persimmon bread	0.013	0.09	< 0.0001
Fresh fruit/winter	−0.025	0.07	< 0.0001
Meals with oil	−0.0068	0.07	< 0.0001
Tobacco use	−0.55	0.06	< 0.0001
Eggs	−0.0026	0.05	< 0.0001
Summary of conditions	−0.064	0.05	0.0003
Dried vegetables/summer	0.0078	0.03	0.0057
Moldy bread	0.021	0.02	0.031
Pickled vegetables/winter	0.0043	0.04	0.0011
Colds/flu in previous 12 months	−0.038	0.01	0.054
Fresh vegetables/summer	0.00064	0.01	0.18
Summary of diseases	0.038	< 0.001	0.56
Pickled vegetables/summer	0.0045	< 0.001	0.61

[a] Linear regression was used to examine the association between the listed variable and the number of teeth lost as a continuous variable. Variables are sorted by descending R^2 value.

Because of strong correlations between age and both tooth loss and cancer incidence, we used several methods to control for age in our Cox proportional hazards regression analyses.

Cox proportional hazards models for risk of upper gastrointestinal cancer

Table 3 presents the results of our analyses of tooth loss and risk of upper gastrointestinal cancer at four sites. We examined the risk associated with any loss of permanent teeth (any *versus* no teeth lost) and found a significantly increased risk in the esophagus and esophagus/cardia. A borderline significantly elevated risk in the gastric non-cardia was also found.

Next, the number of teeth lost was used as a predictor of cancer risk. When we examined the number of teeth lost using a median split to assess risk associated with being in the upper 50th percentile of tooth loss, we saw significantly elevated risk at each tumor location. When we examined the number of teeth lost as a continuous linear variable, we found it was only significantly associated with esophagus/cardia cancers combined (Table 3). When a quadratic term for the number of teeth lost was added to the model, we found that the number of teeth lost was significantly associated with cancer risk at each site except the gastric cardia, where statistical significance was approached ($p = 0.075$) (Table 4). Each quadratic term had a negative parameter estimate, resulting in a diminution of the effect of tooth loss with increasing loss of teeth. To demonstrate this non-linear effect the risk associated with three arbitrary steps in tooth loss, going from 0 to 10 teeth lost, 10 to 20 teeth lost, and 20 to 32 teeth lost, were calculated from the continuous non-linear model and are given in Table 4. In each case only the first step, from 0 to 10 teeth lost, is associated with a significantly increased risk of cancer.

Table 3. Relative risk (95% CI)[a] of upper gastrointestinal cancers associated with tooth loss[b]

Tumor location	Number of cases	Tooth loss variable	RR (95% CI)	*p*-Value
Esophagus	620	Any lost teeth	1.3 (1.0–1.6)	0.037
		Number of teeth lost (median split)	1.3 (1.1–1.6)	0.006
		Number of teeth lost (continuous)	1.1 (1.0–1.2)	0.058
Gastric cardia	431	Any lost teeth	1.1 (0.83–1.4)	0.54
		Number of teeth lost (median split)	1.3 (1.0–1.6)	0.022
		Number of teeth lost (continuous)	1.1 (0.99–1.2)	0.069
Gastric non-cardia	102	Any lost teeth	1.9 (0.97–3.8)	0.062
		Number of teeth lost (median split)	1.8 (1.1–3.0)	0.016
		Number of teeth lost (continuous)	1.1 (0.89–1.3)	0.40
Esophagus/cardia	1051	Any lost teeth	1.2 (1.0–1.4)	0.045
		Number of teeth lost (median split)	1.3 (1.1–1.5)	0.0004
		Number of teeth lost (continuous)	1.1 (1.0–1.2)	0.009

[a] RR (95% CI) and *p*-values come from regression models stratified on age category. Additional adjustment was provided by a continuous age term as well as terms for sex, tobacco use, and alcohol use.

[b] The risk associated with the number of teeth lost (median split) was based on the median number of teeth lost among the entire cohort at baseline (six teeth) and RR (95% CI) reflects risk of cancer based on being in the upper 50% of teeth lost. The risk associated with the number of teeth lost (continuous) is given per 10 teeth lost.

Table 4. Relative risk (95% CI)[a] for upper gastrointestinal cancers calculated from the continuous, non-linear model for tooth loss

Tumor location	LR χ^2 *p*-value[b]	Tooth loss step[c]	RR (95% CI)
Esophagus	0.027	0–10 teeth lost	1.3 (1.0–1.6)
		10–20 teeth lost	1.1 (0.83–1.5)
		20–32 teeth lost	0.90 (0.49–1.7)
Gastric cardia	0.075	0–10 teeth lost	1.3 (1.0–1.7)
		10–20 teeth lost	1.1 (0.89–1.4)
		20–32 teeth lost	0.90 (0.55–1.5)
Gastric non-cardia	0.027	0–10 teeth lost	2.5 (1.2–5.2)
		10–20 teeth lost	2.1 (0.87–5.2)
		20–32 teeth lost	2.0 (0.48–8.4)
Esophagus/cardia	0.0020	0–10 teeth lost	1.3 (1.1–1.6)
		10–20 teeth lost	1.1 (0.81–1.5)
		20–32 teeth lost	0.92 (0.47–1.8)

[a] RR (95% CI) and *p*-values come from regression models stratified on age category. Additional adjustment was provided by a continuous age term as well as terms for sex, tobacco use, and alcohol use.

[b] The LR χ^2 value is the two degrees of freedom test for significance of both the linear and quadratic terms for number of teeth lost.

[c] The tooth loss steps presented are arbitrary and chosen to be representative of the range of potential tooth loss.

Finally, we examined the age at first tooth loss as a predictor of cancer risk. This parameter was added to our Cox proportional hazards model that contained tooth loss and age as continuous variables. We found no association between age at first tooth loss and risk of upper gastrointestinal cancers in this model. The LR χ^2 *p*-values were as follows; esophagus $p = 0.46$, gastric cardia $p = 0.36$, gastric non-cardia $p = 0.84$, and esophagus/cardia $p = 0.25$.

Because this cohort was part of a nutrition intervention trial, we also examined the effects of assignment to each of four vitamin/mineral supplementation groups on risk associated with tooth loss. When examined as modifiers of the associations between tooth loss and upper gastrointestinal cancer, either as main effects or as interactions with tooth loss (median split variable), no significant effects of supplementation group assignment were found.

Due to the strong correlation between tooth loss and age (Table 2) this potential interaction was examined. LR χ^2 *p*-values for the interaction term were: esophagus $p = 0.17$, gastric cardia $p = 0.20$, gastric non-cardia $p = 0.014$, and esophagus/cardia $p = 0.061$. Therefore, we stratified our cohort into three age categories and examined age category-specific effects of tooth loss. Table 5 shows the number of cases, the proportion with lost teeth, the median number of teeth lost, and the age at first loss for each tumor location in the three age categories, <50, 50–59, and ≥ 60 years. As expected, both proportion with tooth loss and the number of teeth lost increased with increasing age. In accordance with our linear regression analysis, age at first tooth loss also

Table 5. Tooth loss variables by tumor location and age category

	Age category 1 (<50 years)	Age category 2 (50–59 years)	Age category 3 (≥60 years)
Esophagus (n)	116	266	238
Lost teeth (% yes)	71	84	95
Number of teeth lost: median (IQR)[a]	4 (7)	8 (13)	18 (20)
Age at first loss: median (IQR)	37 (14)	42 (18)	42 (17)
Gastric cardia (n)	65	191	175
Lost teeth (% yes)	66	83	93
Number of teeth lost: median (IQR)	3 (9)	9 (14)	15 (20)
Age at first loss: median (IQR)	38 (13)	42 (19)	45 (21)
Gastric non-cardia (n)	12	40	50
Lost teeth (% yes)	83	90	92
Number of teeth lost: median (IQR)	3 (8)	11 (12)	13 (19)
Age at first loss: median (IQR)	36 (13)	45 (18)	46 (21)
Esophagus/cardia (n)	181	457	413
Lost teeth (% yes)	69	83	94
Number of teeth lost: median (IQR)	4 (9)	8 (13)	17 (20)
Age at first loss: median (IQR)	37 (14)	42 (19)	44 (20)
Non-cases (n)	11,982	9528	6205
Lost teeth (% yes)	57	82	93
Number of teeth lost: median (IQR)	2 (6)	7 (13)	16 (20)
Age at first loss: median (IQR)	39 (11)	43 (17)	45 (20)

[a] IQR = Size of interquartile range (25th percentile–75th percentile).

Table 6. Relative risk (95% CI)[a] of upper gastrointestinal cancers associated with tooth loss[b]

Tumor location	Number of cases	Age category (years)	RR (95% CI)	*p*-Value
Esophagus	116	<50	1.5 (0.99–2.1)	0.054
	266	50–59	1.3 (0.98–1.6)	0.067
	238	≥60	1.1 (0.82–1.4)	0.67
Gastric cardia	65	<50	1.3 (0.80–2.2)	0.28
	191	50–59	1.3 (0.94–1.7)	0.12
	175	≥60	0.99 (0.73–1.3)	0.96
Gastric non-cardia	12	<50	3.3 (0.85–12.4)	0.084
	40	50–59	1.8 (0.92–3.4)	0.088
	50	≥60	1.0 (0.57–1.8)	0.98
Esophagus/cardia	181	<50	1.4 (1.0–1.9)	0.028
	457	50–59	1.3 (1.0–1.5)	0.017
	413	≥60	1.0 (0.85–1.3)	0.78

[a] RR (95% CI) and *p*-values come from individual regression models for each age category. Additional adjustment was provided by a continuous age term as well as terms for sex, tobacco use, and alcohol use.

[b] Tooth loss represented as median splits of the number of teeth lost by age category. Median splits were based on age category-specific values. For age category 1 (<50 years) median tooth loss = 3 teeth, for age category 2 (50–59 years) median tooth loss = 8 teeth, and for age category 3 (≥60 years) median tooth loss = 17 teeth.

Table 7. Relative risk (95% CI)[a] for upper gastrointestinal cancers associated with tooth loss[b]

Site	LR χ^2 *p*-value[c]	Sex	RR (95% CI)
Esophagus	0.16	Female	1.2 (0.90–1.6)
		Male	1.4 (1.1–1.8)
Cardia	0.98	Female	1.4 (0.94–2.0)
		Male	1.3 (0.95–1.7)
Non-cardia	0.79	Female	2.1 (0.74–5.7)
		Male	1.7 (0.99–3.0)
Esophagus/cardia	0.36	Female	1.2 (1.0–1.5)
		Male	1.3 (1.1–1.6)

[a] RR (95% CI) and *p*-values come from regression models stratified on age category. Additional adjustment was provided by a continuous age term as well as terms for tobacco use and alcohol use.

[b] Median splits were based on overall number of teeth lost among the entire cohort at baseline (six teeth).

[c] LR χ^2 *p*-values are the test for significance of the interaction term.

increased with age at baseline. Table 6 shows the relative risk (RR) (95% CI) associated with the number of teeth lost (median split) by age category at each tumor location. Overall, both the RR and the strength of the association were greatest in the lowest age category. Within each age category, the risk associated with tooth loss as a continuous variable appeared positive and linear at each tumor site (data not shown).

Finally, we examined the potential interaction between sex and tooth loss in the risk of developing these cancers. We found no significant interaction between these factors at any of the cancer sites examined (Table 7). We tested the potential three-way interaction between age, sex, and tooth loss at each site. No significant three-way interactions were found.

Discussion

This report is the first prospective study to assess the association between tooth loss and risk of cancers in the upper gastrointestinal tract. A single previous study demonstrated an association between tooth brushing and esophageal cancer but did not determine the effect of tooth number and was not prospective [4]. Several retrospective studies have shown higher risk of gastric cancer among individuals with poor oral hygiene habits or tooth loss [5–7]. To our knowledge this report also represents the largest report of dentition status in a Chinese population.

Using Cox proportional hazards regression and controlling for potential confounders, we found significant relationships between tooth loss and the risk of developing esophageal squamous cell carcinoma, gastric cardia adenocarcinoma, or gastric non-cardia adenocarcinoma. We saw a significant non-linear relationship between the number of teeth lost and cancer risk in the esophagus and gastric non-cardia. In the gastric cardia a similar, although not statistically significant, pattern was observed. The results showed that the greatest increase in risk from tooth loss occurred with the first teeth lost. Further analysis by age category demonstrated that the effect of tooth loss on upper gastrointestinal cancer risk was primarily confined to the younger cohort members and that no increased risk was associated with tooth loss when the oldest age category was examined separately. We found similar patterns of increased risk at each cancer site. Although the calculated relative risks were of generally modest size, the exposure is ubiquitous (>93% of participants aged ≥60 years had lost at least one tooth) and this suggests that the contribution of tooth loss to the overall disease burden could be significant.

We hypothesize four potential mechanisms whereby tooth loss could increase the risk of upper gastrointestinal cancers. The first proposes that tooth loss is a marker for poorer general health and is not a risk factor itself. We looked for associations between tooth loss and markers of general health using linear regression. Although limited in scope, our survey suggested that,

within this population, tooth loss was not an indicator of relatively poor health. This suggests tooth loss was a specific risk factor, in itself, for upper gastrointestinal cancers. In addition, in Western populations tooth loss may be viewed as a surrogate marker for socioeconomic status (SES) but our population was quite homogeneous with regard to occupation and other measures of SES, precluding this interpretation (data not shown).

The second potential mechanism proposes that loss of teeth leads to alterations in dietary patterns which elevate the risk of cancer. We looked for correlations between tooth loss and dietary intake of 15 foods. Only very weak correlations were found. A previous case–control study in Linxian suggested that a high reliance on corn and wheat as dietary staples increased the risk of esophageal cancer [12]. Unfortunately, we did not have information on corn or wheat intake for our cohort and were unable to assess the impact of tooth loss on the intake of these foods. Conflicting results have been reported regarding fresh vegetable intake and risk of esophageal cancer in Linxian [12, 13]. We saw only very weak associations between fresh vegetable consumption and tooth loss.

A third hypothesis, frequently cited in the esophageal cancer literature [4, 14], is that the way in which people chew and swallow food contributes to esophageal cancer risk. Incomplete chewing and rapid swallowing of large pieces of food might cause irritation or damage to the esophageal epithelium and subsequently increase the risk of cancer. No published studies have attempted to measure this effect and we are unable to directly assess the relevance of this potential mechanism to our findings. However, the shape of the non-linear relationship between number of teeth lost and cancer risk would argue against this hypothesis. Loss of the first few teeth would have a relatively minor effect on chewing efficacy compared to the loss of the last remaining teeth, but our study showed that the loss of the first 10 teeth had the greatest effect on upper gastrointestinal cancer risk.

A final hypothesis suggests that tooth loss increases the risk of upper gastrointestinal cancers through alterations in the oral bacterial flora. Oral bacteria can produce upper gastrointestinal tract carcinogens such as acetaldehyde [15] and nitrosamines [16]. In a study by Nair *et al.*, individuals with poor oral hygiene had an 8-fold increase in the potential to form nitrosamines in the oral cavity [17]. This is thought to occur because the bacteria associated with caries and periodontal disease, such as *Streptococcus mutans*, are efficient reducers of nitrate to nitrite, a necessary step in the *in-vivo* formation of nitrosamines [17]. This endogenous formation accounts for 45–75% of a typical individual's nitrosamine exposure [18]. Furthermore, the level of nitrate reduction in the mouth is the major factor in inter-individual variation in *in-vivo* nitrosamine formation, and antiseptic mouthwashes significantly decrease this formation [16]. An ecologic study has suggested that residents of Linxian have a greater tendency to produce nitrosamines *in vivo* than do populations at lower risk for esophageal cancer [19]. Clearly, more detailed investigations of the links between tooth loss, oral bacteria, nitrosamine formation, and upper gastrointestinal cancer are warranted.

Our analysis demonstrated a distinct effect of age on the risk of upper gastrointestinal cancers conferred by tooth loss. Several explanations may have contributed to this effect. First, over 93% of the individuals in our oldest age category had lost at least one tooth, which may have limited our power to detect an effect of tooth loss on cancer risk in this subgroup. Second, this may represent a birth cohort effect. Changes in diet, water supply, and other environmental factors in Linxian between the oldest age group's and the youngest age group's lifespans may have contributed to different risks associated with tooth loss. Third, the age group differences may have been due to circumstances at a sensitive age of exposure when tooth loss most strongly confers an increased risk of developing upper gastrointestinal cancers.

In summary, we examined the association between tooth loss and risk of upper gastrointestinal cancers in a large prospective study. We found significantly elevated risk of cancer in the esophagus, gastric cardia, and gastric non-cardia in those who had lost teeth. This increased risk was most strongly associated with the loss of the first few teeth and was primarily confined to the younger members of our cohort. Our findings raise the possibility that tooth loss may increase risk of upper gastrointestinal cancers through associated changes in bacterial flora which can lead to increased exposure to carcinogens such as nitrosamines.

References

1. Zheng TZ, Boyle P, Hu HF, *et al.* (1990) Dentition, oral hygiene, and risk of oral cancer: a case–control study in Beijing, People's Republic of China. *Cancer Causes Control* **1**: 235–241.
2. Bundgaard T, Wildt J, Frydenberg M, Elbrond O, Nielsen JE (1995) Case–control study of squamous cell cancer of the oral cavity in Denmark. *Cancer Causes Control* **6**: 57–67.
3. Zheng W, Blot WJ, Shu XO, *et al.* (1992) Risk factors for oral and pharyngeal cancer in Shanghai, with emphasis on diet. *Cancer Epidemiol Biomarkers Prev* **1**: 441–448.
4. Wang YP, Han XY, Su W, *et al.* (1992) Esophageal cancer in Shanxi Province, People's Republic of China: a case–control study in high and moderate risk areas. *Cancer Causes Control* **3**: 107–113.
5. Watabe K, Nishi M, Miyake H, Hirata K (1998) Lifestyle and gastric cancer: a case–control study. *Oncol Rep* **5**: 1191–1194.

6. Demirer T, Icli F, Uzunalimoglu O, Kucuk O (1990) Diet and stomach cancer incidence. A case–control study in Turkey. *Cancer* **65**: 2344–2348.
7. Wolff G, Lauter J (1976) On epidemiology of gastric cancer. *Arch Geschwulstforsch* **46**: 1–14.
8. Zhang ZX, Li BY, Jin SS (1990) Epidemiologic trends of esophageal cancer in Linxian. *Research on esophageal cancer prevention and treatment (Shi Guan Ai Fang Zhi Yan Jiu - Linxian)* **1**: 1–14.
9. Li B, Taylor PR, Li JY, *et al*. (1993) Linxian nutrition intervention trials. Design, methods, participant characteristics, and compliance. *Ann Epidemiol* **3**: 577–585.
10. Blot WJ, Li JY, Taylor PR, *et al*. (1993) Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst* **85**: 1483–1492.
11. Limburg PJ, Qiao Y-L, Mark SD, *et al*. (2001) *Helicobacter pylori* seropositivity and subsite-specific cancer risks in Linxian, China. *J Natl Cancer Inst* **93**: 226–233.
12. Li JY, Ershow AG, Chen ZJ, *et al*. (1989) A case–control study of cancer of the esophagus and gastric cardia in Linxian. *Int J Cancer* **43**: 755–761.
13. Yu Y, Taylor PR, Li JY, *et al*. (1993) Retrospective cohort study of risk-factors for esophageal cancer in Linxian, People's Republic of China. *Cancer Causes Control* **4**: 195–202.
14. Yang CS (1980) Research on esophageal cancer in China: a review. *Cancer Res* **40**: 2633–2644.
15. Muto M, Hitomi Y, Ohtsu A, *et al*. (2000) Acetaldehyde production by non-pathogenic *Neisseria* in human oral microflora: implications for carcinogenesis in upper aerodigestive tract. *Int J Cancer* **88**: 342–350.
16. Shapiro KB, Hotchkiss JH, Roe DA (1991) Quantitative relationship between oral nitrate-reducing activity and the endogenous formation of N-nitrosoamino acids in humans. *Food Chem Toxicol* **29**: 751–755.
17. Nair J, Ohshima H, Nair UJ, Bartsch H (1996) Endogenous formation of nitrosamines and oxidative DNA-damaging agents in tobacco users. *Crit Rev Toxicol* **26**: 149–161.
18. Tricker AR (1997) N-nitroso compounds and man: sources of exposure, endogenous formation and occurrence in body fluids. *Eur J Cancer Prev* **6**: 226–268.
19. Wu Y, Chen J, Ohshima H, *et al*. (1993) Geographic association between urinary excretion of N-nitroso compounds and oesophageal cancer mortality in China. *Int J Cancer* **54**: 713–719.